Remarks

The Office Action dated October 19, 2007 has been carefully reviewed and the following amendments and comments are made in response thereto. In view of the above amendments and following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. Applicants have cancelled all of the withdrawn claims without prejudice or disclaimer of Applicants' right to pursue this cancelled subject matter in one or more divisional applications.

Applicants have amended the independent claims to incorporate features present in the dependent claims. Applicants thus submit that no new subject matter has been added by these amendments and that they are fully supported by the text of the specification. Further, all of the amendments are derived from dependent claims which the Examiner considered to be part of the elected invention. Applicants therefore further submit that all of the pending claims are drawn to the elected invention.

The drawings were objected to for recitation of nucleic acid and amino acid sequences without sequence identifiers. The Examiner also requested that the Applicant comply with the sequence rules by inserting the sequence identification numbers of all of the sequences recited within the claims and specification. Applicants have amended the specification to include all of the available sequence identifiers where applicable. Applicants specifically note the amendments to the figure legends in response to the Examiner's comments.

Objections to the Claims

Claims 2-4 and 7-14 were objected to because of the recitation "a recombinase" in these dependent claims. Applicants have amended these and other dependent claims to recite "the recombinase" as applicable and therefore request that the objection be withdrawn.

Claims 18-23 and 28-42 were objected to because of the recitation "a hybrid recombinase" in these dependent claims. Applicants have amended these and other dependent claims to recite "the hybrid recombinase" as applicable and therefore request that the objection be withdrawn.

Claims 47 and 52-59 were objected to because of the recitation "a catalytic domain" in these dependent claims. Applicants have amended these and other dependent claims to recite "the catalytic domain" as applicable and therefore request that the objection be withdrawn.

Claim 8 was objected to for a typographical error. This claim has been amended to remove the typographical error. Applicants therefore request that the objection be withdrawn.

Rejection of the Claims under 35 U.S.C. 112 (second paragraph)

Claims 8-11 and 53-56 were rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. These claims recite the terms "1,3 or 1,2 or 2,3 interface" which is unclear to the Examiner. The Examiner purports that the specification does not define what this phrase means. Applicants disagree and note that these terms are well known to one of skill in the art of serine recombinases and are also adequately defined in the specification. The 1,2 and 2,3 resolvase dimer interactions are disclosed in the specification at least at page 3 beginning at line 21. Further, those amino acid residues forming the 1,2 interface are disclosed in the specification at page 46, beginning at line 8 and are also listed in Table 1 on page 61. Amino acid residues of the 2,3 interface are disclosed in the specification at page 49 beginning on line 18 and in Figure 4. Applicants thus submit the recited terms are adequately defined in the specification such that they would know their meaning and scope and request that the rejection be withdrawn.

Claims 18-23, 23-38 and 68 were also rejected as being indefinite in the recitation of "said catalysing" lacking antecedent basis. Applicants have amended claim 18 to remove "said" from the claim rendering the rejection is moot. Applicants therefore request withdrawal of this rejection.

Rejections of the Claims under 35 U.S.C. 112 (first paragraph)

Claims 1-4, 7-14, 18-22, 28-42, 46-47, 52-59 and 67-68 were rejected as failing to comply with the written description requirement. The Examiner purports that the claims were not described in the specification in such a way as to reasonably convey to the skilled artisan that the inventors had possession of the claimed invention at the time of filing. Specifically, the Examiner considers the lack of description in the specification of representative species encompassed by the genus of proteins of the claims to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize that Applicants were in possession of the claimed invention (see page 8 of Office Action).

Applicants disagree and note that the specification provides extensive guidance of the structural features (both secondary and tertiary) of serine recombinases which are important for the present invention. These features are described with reference to both Tn3 resolvase and γδ resolvase. Further, the serine recombinase family of related enzymes is well known in the art and, as described on page 12 of the specification, members of this protein family share significant sequence identity. Figure 1 displays an

alignment of fourteen (14) separate and distinct serine recombinases, and indicates that a number of residues are conserved across different members of this protein family. Accordingly, it is expected that the effects observed from mutation of the Tn3 resolvase may also be expected in other members of the serine recombinase protein family. For example, mutation of the corresponding residues in a Sin recombinase from *Staphylococcus aureus*, which is functionally quite distant from Tn3 resolvase, produces entirely predictable results. Such results are discussed on page 13 of the specification beginning at line 20.

For these reasons, it is submitted that the specification adequately discloses a representative number of species of serine recombinases such that the skilled artisan would recognize that Applicants were in possession of the claimed invention at the time of filing. Applicants respectfully request withdrawal of the rejection.

The Examiner has also rejected claims 1-4, 7-14, 18-22, 28-42, 46-47, 52-59 and 67-68 because the specification does not provide enablement for any serine (or hybrid) recombinase, or catalytic domain from a serine recombinase, from any source. The Examiner purports that while recombinant and mutagenesis techniques are known, it is not routine to screen for multiple positions where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity (see Office Action at page 9, line 21).

Applicants disagree and note that those residues tolerant to modification are specified in the amended claims, and the specification clearly describe these residues with reference to the amino acid sequence of Tn3 resolvase and also with reference to structural characteristics such as their position at the 1,2 interface (see, for example, Figure 6). High resolution crystal structures have been obtained for several members of the serine recombinase family, and these may be used in conjunction with biochemical structural data to enable the skilled artisanto easily identify the residues in other serine recombinases that correspond to the Tn3 residues which, when mutated, cause hyperactivity.

Applicants thus submit that the specification does disclose sufficient information to enable the skilled artisan to practice the claimed invention using any catalytic domain and any DNA binding domain of any serine recombinase. Further, the specification discloses significant guidance of the features necessary for a heterologous DNA binding domain which make it applicable to the hybrid recombinases of the present invention (see, for example, pages 18 to 21 of the specification). Accordingly, Applicants request that the rejection of the claims for lack of enablement be withdrawn in view of the aforementioned remarks.

Rejection under 35 U.S.C. 102(b)

Claims 1-2, 7-8, 10-11, 14, 46-47, 52-53, 55-56 and 59 were rejected as being anticipated by Arnold *et al.* (Arnold). Without acquiescing to the merits of the rejection and solely for the purpose of advancing prosecution, Applicants have amended the claims to provide for at least one other mutation that was not disclosed in the cited reference. In view of these claim amendments, Applicants respectfully request withdrawal of the rejection.

Claims 1-4, 7-12, 14, 46-47 and 52-59 were rejected as being anticipated by Sarkis *et al.* (Sarkis). Without acquiescing to the merits of the rejection and solely for the purpose of advancing prosecution, Applicants have amended the claims to provide for at least one other mutation that was not disclosed in the cited reference. In view of these claim amendments, Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. 103

Claims 18-35, 38-39, 41-42, 57 and 68 were rejected as being obvious in view of Arnold, Sarkis and Jamieson et al. (Jamieson). The Examiner purports that by combining the teachings of Arnold, Sarkis and Jamieson, it would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the DNA binding domain of Tn3 resolvase of Arnold and Sarkis with the DNA binding domain of Jamieson to make a hybrid recombinase (see Office Action at page 15, line 16).

Applicants first note that these same claims (18-22, 38-39, 41-42) are also rejected for lack of enablement under 35 U.S.C. 112 (first paragraph). As the Examiner is aware, to establish a *prima facie* conclusion of obviousness, the Examiner must combine prior art elements according to known methods to yield predictable results (see M.P.E.P. 2143). Here, the Examiner has stated on the record that it is not routine in the art to screen for multiple substitutions as encompassed by the instant claims and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity are limited in any protein and the result of such modifications is unpredictable (see Office Action at page 9, line 21). It is therefore unclear to Applicants how the Examiner can maintain that these claims are obvious while in the same Office Action state that the same claims are not enabled by the specification. Clearly the Examiner is picking an choosing embodiments of the claims to support these rejections and not considering the claims as a whole. Applicants therefore submit that the Examiner has not established a *prima facie* case of obviousness in his

rejection of the claims.

Further, Applicants submit that when looking to identify additional hyperactive recombinases, the skilled artisan would have disregarded the quadruple mutant disclosed by Arnold. This reference fails to disclose or even suggest any recombinase mutated at G101 which is hyperactive. Arnold expressly states that the D102Y substitution produces the strongest recombinase activity of all of the mutants isolated, and the quadruple mutant is desired as having sufficient activity to have allowed it to be detected. Arnold actually teaches against the claimed invention. The skilled artisan considering the teachings of Arnold could quite reasonably believe that any hyperactivity effect caused by D102Y is actually supressed in the quadruple mutant, and therefore would not have expected G101 substitutions to impart any hyperactive effect. Further, there are certainly no suggestions in Arnold that substitution of any residue other than D102 influences the level of recombinase activity and this deficiency is certainly not overcome by Sarkis. Accordingly, Applicants submit that the creation of the hyperactive recombinases carrying a substitution at G101 but not mutated at M103 or D102 is not obvious in view of the cited references.

Applicant further submit that the claimed hybrid recombinases of the present invention are derived from the surprising and unexpected finding that attachment of an unrelated DNA binding domain to a mutated catalytic domain is sufficient to restore catalytic activity. Prior to the filing of the present application, it was known that the N-terminal domain of serine recombinases has no catalytic activity on its own (see specification at page 15). Thus, prior to the filing of the present application, it would have been expected that the natural DNA binding domain plays some essential role in recombinase activity. While the DNA binding domain may not participate directly in the reaction, it may be indirectly influential because of conformational changes which occur in bound versus unbound states. The inventors have identified the unexpected and surprising property that N-terminal catalytic domain activity may be restored by attachment of any unrelated DNA binding domain, and this property is neither taught nor suggested in the prior art. Applicants note that evidence of an unexpected property is evidence of non-obvious (see M.P.E.P 716.02(a)). In view this, Applicants request that the rejection of the claims as being obvious in view of the cited references be withdrawn.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Dated: **March 19, 2008**
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Respectfully submitted,
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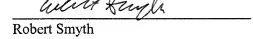

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